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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,648	12/19/2001	Heather J. Belmont	49663 (71758)	2636

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
12/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/024,648	BELMONT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,30,31,38,39,41-45,47 and 112-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,30,31,38,39,41-45,47 and 112-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered. Applicant's amendment and response filed concurrently with the RCE have also been entered. Claims 3, 8-29, 32-37, 40, 46, and 48-111 are canceled. New claim 114 has been added. Claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-114 are pending and currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

It is again noted that claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-113 continue to read broadly on any non-human transgenic animal. The claims have been and continue to be examined in view of the elected subject matter, i.e. a transgenic mouse. It is further noted that the species of mouse was elected **without** traverse, and that neither the elected species nor the generic claims are found to be allowable.

Claim Rejections - 35 USC § 103

The rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240, is maintained and further applied to new claim 114. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant reiterates their argument that none of the cited references provide the requisite teaching of a mouse comprising human TCR loci that are capable of undergoing productive rearrangement. Specifically, the applicant argues that the constructs taught by McMurry et al. were designed with mutated V gene segments such that the rearranged TCR transgene does not express functional TCR protein products, and that the Lauzurica and Krangel reference previously cited by the applicants teach that the transgenic mice in McMurry were intentionally designed not to produce the transgenic TCR protein product so as not to unfavorably affect normal thymic development. The applicant concludes that therefore one of skilled in the art would not be motivated to make a transgenic animal which expresses a productively rearranged TCR because it would adversely affect normal thymic development. In response, the Lauzurica and Krangel publication previously submitted with the response of 9/18/06, only reiterated the same information found in McMurry et al., that the V region genes were mutated to prevent rearranged transcripts from encoding "functional TCR protein and thereby influencing thymic development", see page 1914, column 2 of Lauzurica and Krangel

(June, 1994) J. Exp. Med, Vol. 179, 1913-1921, submitted by applicants as Appendix A. There is no statement that such an expression would "unfavorably" or "adversely" affect thymic development as argued by the applicants. In fact, the original Lauzurica and Krangel publication which gives the first description of transgenic mice comprising a human TCR delta locus, Lauzurica and Krangel (January, 1994), Vol. 179, pages 43-55, specifically states the reason why the added mutations to the V gene segments in the construct. On page 45, under the heading "strategy", the authors state, "[w]e wanted the construct to serve as an innocuous reporter that would not influence the rearrangement of endogenous TCR genes via the process of allelic exclusion". Thus, contrary to applicant's arguments, McMurry, as evidenced by the original Lauzurica and Krangel paper published in January of 1994 cited in McMurry et al., does not teach or suggest the expression of a human TCR would negatively influence thymic development. Instead, the authors of Lauzurica and Krangel and McMurry et al. were trying to answer the question of whether some precommitment to the alpha/beta or gamma/delta cell lineage dictates gene rearrangement or whether gene rearrangement dictates cell lineage development. Further, the fact that they felt the need to mutate the V region genes in the human TCR transgene construct indicates that the authors clearly expected that transgenic mice comprising the human TCR delta transgene would in fact productively rearrange this loci and express human TCR delta chains thus inducing allelic exclusion. Therefore, the applicant's arguments regarding the teachings of McMurry et al. are not persuasive.

Regarding the discussion in the previous office action of the similarities between Ig loci rearrangement and TCR rearrangement in response to applicant's previous argument that the complexity of the TCR loci and the complexity of the developmental regulation of

rearrangement of the αβ TCR and γδ TCR loci would preclude a reasonable expectation to success in achieving productive rearrangement with human α or β TCR loci, the applicant now states that the different developmental pathways used by B cells versus T cells precludes comparison between Ig loci and TCR. In response, the applicant is again pointed to the teachings of McMurry et al, who teaches that the TCR and Ig (immunoglobulin) loci are similar in structure and that rearrangement of the TCR and Ig loci utilizes the same recombination machinery. Like TCR β loci resembles the Ig heavy chain loci in that both comprise numerous V region genes, including pseudogenes, D region genes, J region genes, and C region genes, and the TCR α loci resembles the Ig light chain kappa loci in that both comprises numerous V region genes, including pseudogenes, J region genes, and a C region gene. Furthermore, it is reiterated that the prior art of record, WO 98/24893 and US. Patent 6,150,584, both cited by applicants in IDS submissions, provides clear evidence of the production of transgenic mice with deletions in the endogenous immunoglobulin heavy and kappa light chain loci and comprising unrearranged transgenes comprising the human heavy chain and kappa light chain immunoglobulin loci which are fully capable of productive rearrangement of the transgenes resulting in the expression of functional antibodies. As such, the teachings of McMurry et al. regarding the similarities between the Ig and TCR loci and the state of the art of transgenic mice comprising unrearranged heavy and light chain loci would have led the skilled artisan to have a reasonable expectation of success that the presence of unrearranged TCR α or β TCR loci in transgenic mice would lead to productive rearrangement and expression of functional αβ TCR in T cells.

Regarding Littman et al., the applicant states that this reference only provides a general description and does not enable the production transgenic mice comprising human TCR alpha

and beta loci capable of productively rearranging these loci, and that Rowen et al. and Rack et al. do not overcome the limitations of the teachings of Littman et al. and McMurry et al. In response, the rejection of record states that Littman et al. provides general teachings which are supplemented by the teachings of Mombaerts et al., McMurry et al., Rack et al., and Rowen et al. As discussed in previous office actions, Littman et al. teaches general methods for producing transgenic non-human animals, preferably mice, which express human lymphocyte transduction proteins and lack expression of the cognate murine lymphocyte transduction protein as a result of inactivation of the endogenous lymphocyte transduction gene loci (Littman et al., abstract, columns 4-6). Littman et al. further teaches that the lymphocyte transduction gene loci and lymphocyte transduction genes include the T cell receptor genes and particularly the T cell receptor alpha and beta gene products (Littman et al., columns 8-9). Littman et al. further provides substantial guidance for making transgenic mice which comprise human lymphocyte transduction transgenes in their genome and which have inactivated cognate lymphocyte transduction transgenes (Littman et al., columns 14-36).

Littman et al. differs from the instant invention by not specifically describing a transgenic mouse in which the TCR loci are inactivated and human unrearranged TCR V, D and/or J, and C genes have been inserted into the genome. It is noted that although Littman et al. suggests and provides motivation for inactivating the TCR loci of mice and inserting human TCR loci, Littman et al. exemplifies CD4 loci, not TCR loci. However, at the time of filing, transgenic mice which expressed unrearranged human T cell receptor loci and mice with have deletions in the endogenous TCR loci were described and available. Mombaerts et al. for instance teaches 3 different strains of mice which have inactivating deletions in the TCR alpha loci, TCR beta loci,

or TCR delta loci (Mombaerts et al., page 275). In particular, note that Mombaerts teaches deleting the D,J, and C genes of the endogenous TCR beta locus (Mombaerts et al., page 3085, Figure 1). Mombaerts et al. also teaches double knock-out mice produced by crossing TCR beta and TCR delta knock-out mice (Mombaerts et al., page 275). McMurry et al. further supplements Littman et al. by teaching transgenic mice carrying the human unrearranged TCR delta gene minilocus. McMurry et al. teaches that the human TCR delta gene minilocus comprises unrearranged human multiple V, D, J, and C gene segments (McMurry et al., page 4553-4554). McMurry et al. also teaches that these mice are capable of rearranging the human TCR delta gene locus. Further as discussed in detail above, the fact the particular human TCR delta loci transgene construct disclosed by McMurry et al. has mutated V region genes such that successfully rearranged V-D-J-C protein product is not produced does not negate or teach away from the fact that McMurry et al. exemplifies that human TCR loci can successfully rearrange in a transgenic mouse.

In addition, Rowen et al. and Rack et al. were cited for teaching the complete 685-kB DNA sequence of the human beta TCR locus and a YAC containing 70% of the TCR alpha locus including multiple TCR alpha V genes, all of the J genes and the C alpha gene respectively (Rowen et al., page 1755-1756, and Rack et al., page 1233-1234 and Figure 1). Please note as well in regards to claim 114, that Rowen et al. clearly teaches the complete human beta TCR locus, which would therefore include all the human TCR beta loci genes. Therefore, based on the teachings and motivation provided by Littman et al. for making transgenic mice which contain human lymphocyte transduction loci, such as the TCR alpha and beta loci, and in which the endogenous lymphocyte transduction loci is inactivated, the teachings of Rowen et al. and Rack

et al. that nucleic acids encoding the unrearranged human TCR alpha and beta loci were well known, and the teachings of McMurry et al. that transgenic mice comprising unrearranged human TCR loci could be effectively produced and that the human TCR loci were capable of rearrangement in mice, it would have been *prima facie* obvious to the skilled artisan to use the nucleic acids taught by Rowen et al. and Rack et al. to make transgenic mice as suggested by Littman et al. and to breed these transgenic mice with any of the TCR loci knock-out mice taught by Mombaerts et al. in order to produce a transgenic mouse in which the endogenous TCR alpha, and/or beta, and/or delta loci are inactivated and which contain the unrearranged human TCR alpha and beta loci. Further, based on the substantial direction provided by all of Littman et al., Mombaerts et al., and McMurry for making transgenic and knock-out mice, the successful demonstration by McMurry et al. that transgenic mice comprising unrearranged human TCR loci can rearrange the human loci, and the high level of skill in breeding and crossing mice, the skilled artisan would have had a reasonable expectation of success in making a transgenic mouse comprising an inactivated endogenous TCR loci and comprising human unrearranged TCR alpha and beta loci, where the loci are capable of productive rearrangement.

Therefore, for reasons of record and the discussion above, the rejection stands.

Applicant's addition of new claim 114 has necessitated the following new grounds of rejection under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 114 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. New claim 114 depend on claim 1, 112, or 113 and adds the limitation, "wherein the human TCR alpha or beta loci contain all of the gene elements". There is a lack of antecedent basis for "the gene elements" as none of claims 1, 112, or 113 recite "gene elements". There is further a lack of antecedent basis for "human TCR alpha or beta loci " in the embodiment where claim 114 depends on claim 113, as claim 113 refers to a "human T –cell receptor beta chain transgene" or a "human T-cell receptor alpha chain transgene" and not loci. Further, it is unclear what the metes and bounds of "all of the gene elements" encompasses as it is unclear whether the "gene elements" indicated refers to human TCR alpha and beta V, D, J, and C gene segments alone; whether it is intended to include all the V, D, J, and C gene segments plus all the regulatory elements present in either loci, or whether the other "genes" are to be included.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note

that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633